Declaration under 37 C.F.R. § 1.132

I, Prof. Dr. Andreas Plückthun, declare and say:

1. I am a named inventor of the subject matter claimed in United States Patent Application Serial No. 09/232,290 ("the Application").

2. I have received a Ph.D. in Chemistry and have worked in the field of protein engineering and particularly antibody engineering for 17 years. My curriculum vitae is attached as Appendix A.

3. I understand that, in one aspect, the invention claimed in the Application covers a DNA sequence encoding an antibody molecule or functional fragment thereof, which contains at least one variable domain and a modification of an inter-domain interface, as compared to a corresponding interdomain interface of a parent antibody

4. I also understand that, in another aspect, the claimed invention is directed to a DNA sequence encoding an antibody molecule or functional fragment thereof, which contains a variable heavy (or light) domain and a modified former interface between the variable heavy (or light) domain and constant heavy (or light) domain of a parent antibody molecule.

5. I further understand that, in yet another aspect, the claimed invention is directed to a DNA sequence encoding a functional antibody fragment, which contains a variable heavy domain, a variable light domain, and a

modification of an inter-domain interface in the variable heavy and/or variable light domain, as compared to a corresponding inter-domain interface of a parent antibody.

6. I also understand that in each of the DNA sequences described in paragraphs 3-5 above, the respective "modification" results in the claimed antibody (or functional fragment thereof) demonstrating increased hydrophilicity as compared to the corresponding parent antibody; and the first variable domain ("variable heavy domain," as referred to in paragraph 5) is capable of interacting with a second variable domain ("variable light domain," as referred to in paragraph 5) to form a functional antibody molecule or functional fragment thereof (collectively, "the claimed invention").

7. I have reviewed the relevant provisions of the Office Actions dated June 19, 2000, December 5, 2000, June 19, 2001, May 31, 2002, and November 19, 2002; and I understand that the Examiner asserts that the claimed invention is anticipated by Johnson et al. WO 92/01787 ("Johnson").

8. I further understand that the basis for the Examiner's position is that: (i) the allegedly anticipated claims do not exclude an inter-domain interface between the heavy and light variable regions in certain recombinant antibody molecules such as single chain antibodies (see November 19, 2002 Office Action at page 2, penultimate para), and (ii) Johnson allegedly teaches antibody fragments, e.g. scFv and Fab (see id. at page 3, lines

1-3), that have modified interfaces between immunoglobulin domains derived from different chains, i.e. "VH from the heavy chain and VL from the light chain" (June 19, 2001 Office Action at page 4, lines 5-6).

9. In my professional opinion, however, Johnson does not teach antibody formats that contain two variable domains, i.e. a variable light and variable heavy domain. As objective evidence of my view regarding the teachings of Johnson, I note the following excerpts from Johnson:

(a) Johnson teaches modifying amino acid residues in "the region on a given heavy or light chain of an immunoglobulin which associates with the complementary heavy or light chain" (page 13, lines 19-22) (emphasis added);

(b) The reason Johnson made the modifications referred to in paragraph (a) was "to ameliorate... problems associated with single variable domain binding members" (page 2, line 27 through page 3, line 1), namely "problems... characteristic of antibody fragments containing unpaired single domains" (page 2, lines 23-26) (emphasis added).

(c) Specifically, Johnson describes mutating residues H37, H39, H45, H47, H91, H93 and H103 in the variable heavy domain of a single variable domain binding member, since these residues normally interact with the VL counterpart domain (see page 23, lines 4-7) (emphasis added).

7. Thus, the residues that Johnson specifically teaches to modify play a role in the interaction between an antibody variable domain and its variable domain counterpart.

8. A skilled worker would, accordingly, expect that any of such modification(s) to an antibody variable domain would prevent the interaction between this antibody variable domain and its variable domain counterpart. For example:

   (a) the formation of Fab and $F(ab^1)_2$ formats, as outlined by Johnson at page 13, line 3, would be impossible following Johnson's teachings, since each of these two formats requires, by definition, the interaction between a variable heavy and a variable light domain; and

   (b) the formation of a functional scFv antibody format, as outlined by Johnson at page 13, line 3, also would be impossible following Johnson's teachings, since this format requires that the two variable domains, which are expressed within a single polypeptide chain, must interact with each other.

9. In other words, the skilled artisan would conclude that the variable domain modifications Johnson teaches (in particular, the modifications referred to in paragraph 6(c) above) would not enable the production or formation of any antibody fragment containing an antibody variable domain that interacts with, or is capable of interacting with, another variable domain

to thereby form a functional antibody or fragment thereof, e.g. Fab, and $F(ab^1)_2$.

10. All statements made herein of my knowledge are true and all statements made on information and belief are believed to be true; and further, these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any document or any registration resulting therefrom.

Date: 25.4.03

Andreas Plückthun, PhD